Programmed Ribosomal Frameshifting and Codon Usage Bias

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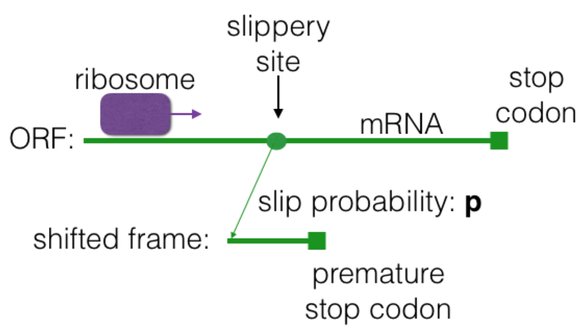
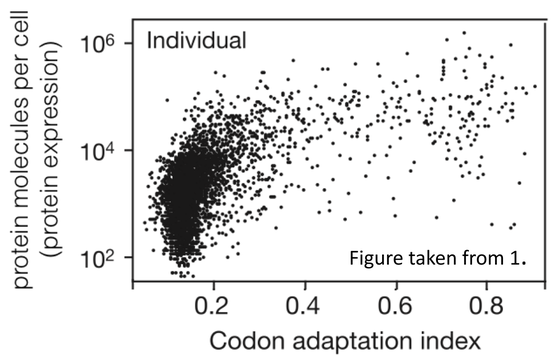
-1 Programmed Ribosomal Frameshifting affects translational efficiency hypothesis (TEH)

Background

- -1 Programmed Ribosomal Frameshifting (-1 PRF) is used for protein expression regulation
- Translation Efficiency Hypothesis: codon usage adapted to tRNA abundance to match increased protein expression demand
- Codon usage bias (CUB) associated with protein expression



-1 PRF is a translational disruption phenomenon at slippery sites.

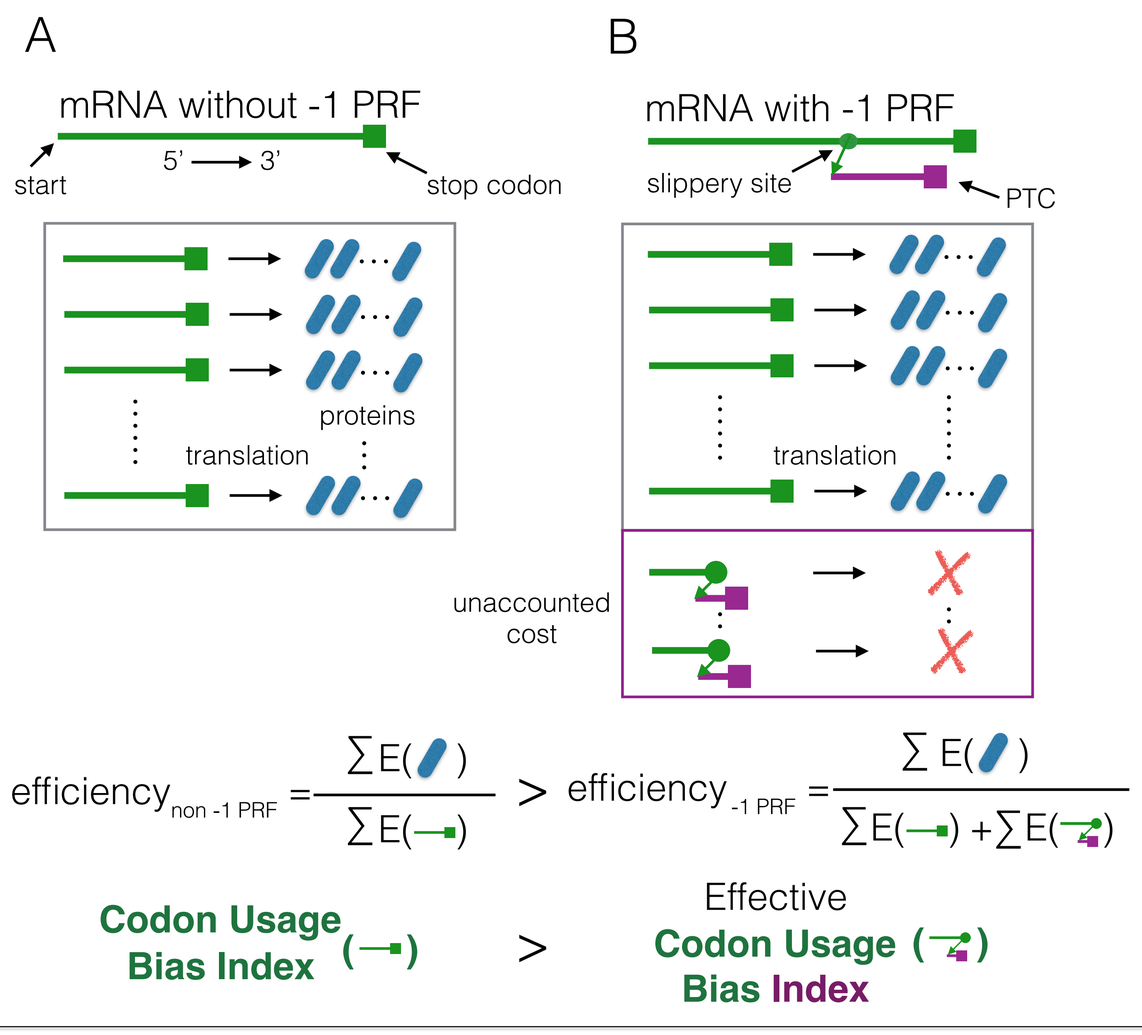


Codon usage bias (CUB) index is associated with protein expression

Our Vision:
Understand how -1 PRF affects codon usage bias (CUB)

- Is there a cost to -1 PRF that affects CUB composition
- Do CUB indices appropriately reflect the translational efficiency of mRNA?
- How can we correct for the translational mismatch?
- Does the TEH hold after correction?

-1 PRF changes meaning of CUB index

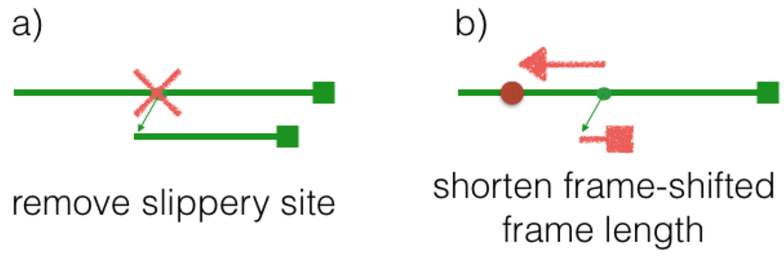


$$\text{efficiency}_{\text{non -1 PRF}} = \frac{\sum E(\text{●})}{\sum E(\rightarrow)} > \text{efficiency}_{\text{-1 PRF}} = \frac{\sum E(\text{●})}{\sum E(\rightarrow) + \sum E(\text{↘})}$$

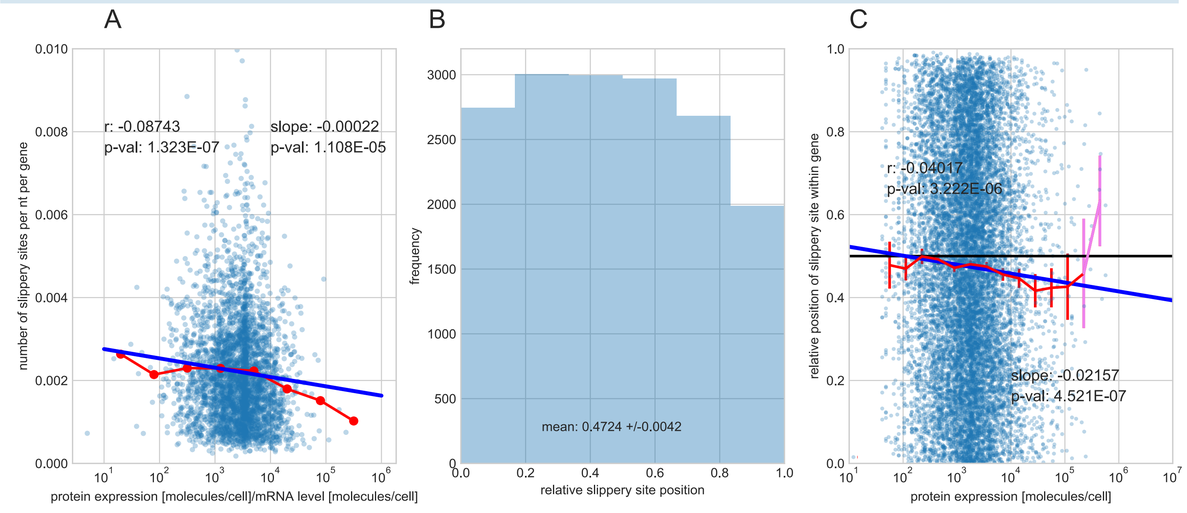
Codon Usage Bias Index (→) > Effective **Codon Usage Bias Index** (↘)

Evidence for a cost to -1 PRF maintenance

Independent effects arising from a -1 PRF cost;
If protein expression demand increases, we expect that evolution will



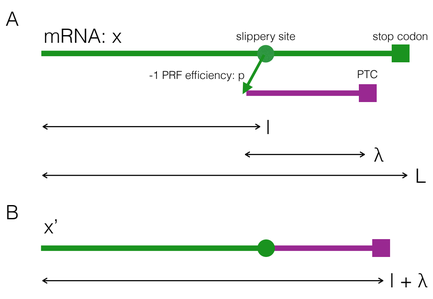
Hypothesis testing:



Three independent test support notion of a cost to -1 PRF maintenance.

Retesting the translational efficiency hypothesis (TEH) under new codon usage bias index

A A -1 PRF corrected codon usage bias index



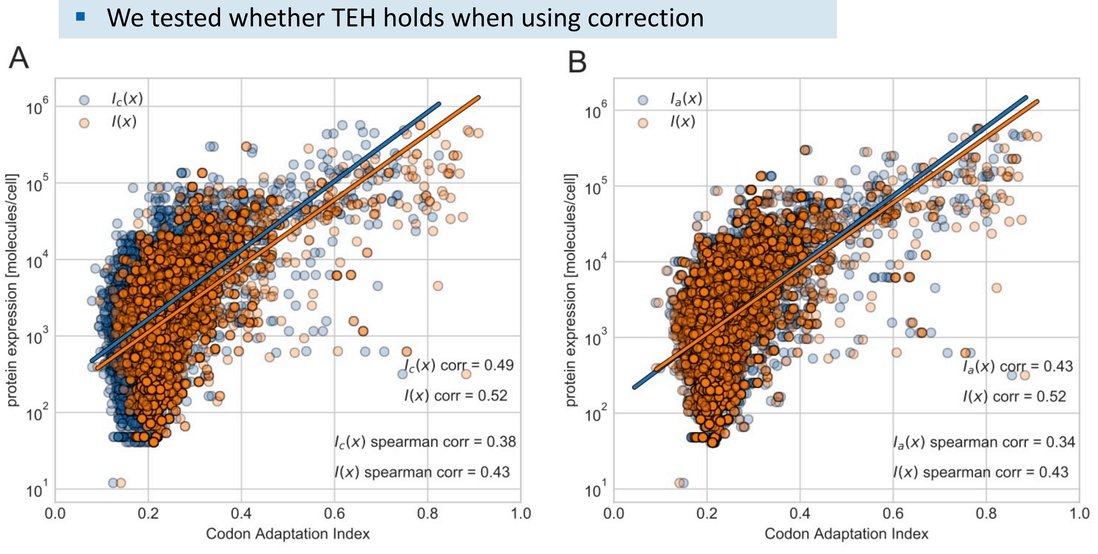
$$\hat{I}_c(x) \doteq \left(1 + \frac{l + \lambda + \pi\left(\frac{p}{1-p}\right)}{L}\right)^{-1} I(x).$$

$$I_a(x) \doteq (1-p)I(x) + pI(x').$$

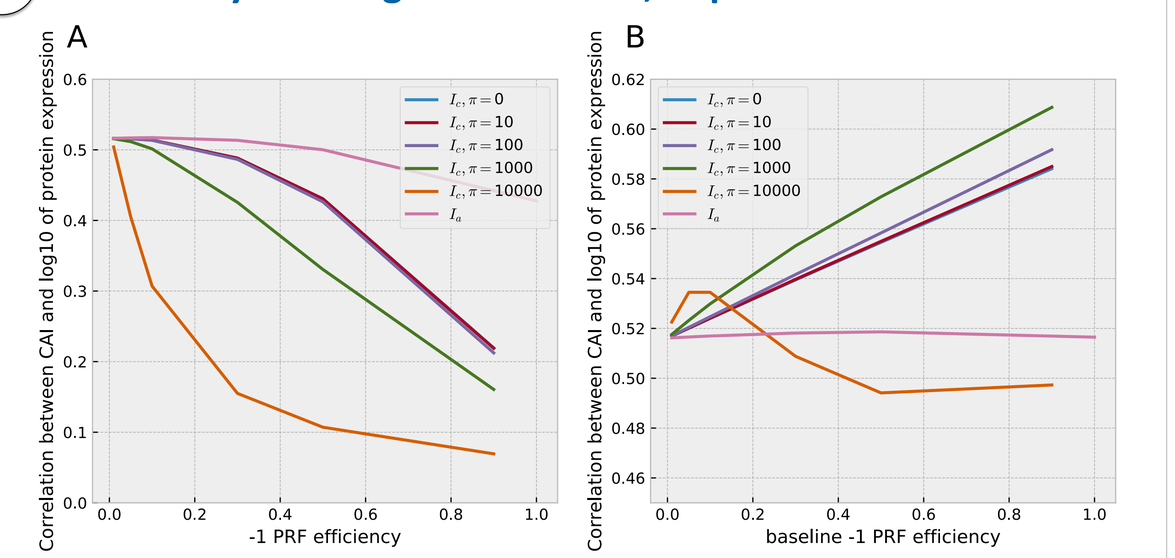
I(x) is any codon usage bias index. π is the cost of translation interruption. Else: as in left fig.

B Translational efficiency hypothesis (TEH) is supported by data

- We tested whether TEH holds when using correction



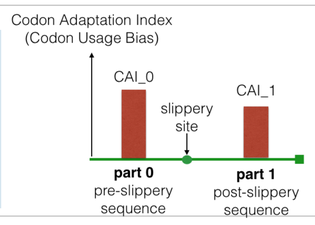
C TEH is only challenged in extreme, implausible scenarios



- **A) Associations** between index and protein expression decline for increasing -1 PRF efficiency (p)
- The decline is insufficient to challenge the TEH
- **B) Association** between index and protein expression (P) improve when more plausible biological relation is assumed: $p(P) = p_b / \log_{10}(P)$

Conclusion

- The translational efficiency hypothesis is strengthened
- The cost of -1 PRF is likely to affect codon usage bias in different ways
- -1 PRF can be used as "natural experiment" to study codon usage bias.
  - Perhaps can be used to differentiate between selection for accuracy and efficiency in certain contexts



References
1. Ghaemmaghami et al., *Global analysis of protein expression in yeast*, 2003, nature

Acknowledgments
The project is supported by SystemsX.ch and evaluated by the Swiss National Science Foundation (SNSF).

SystemsX.ch
The Swiss Initiative in Systems Biology

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